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## WJG 20<sup>th</sup> Anniversary Special Issues (1): Hepatocellular carcinoma

# Current surgical treatment strategies for hepatocellular carcinoma in North America

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downstage HCC to within Milan criteria or as a bridge to transplantation in patients on transplant wait list.

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**Key words:** Hepatocellular carcinoma; Liver transplantation; Liver resection; Transarterial chemoembolization; Radiofrequency ablation

**Core tip:** This is a review article on the current strategies for the management of hepatocellular carcinoma in North America. This article covers the evolution of techniques and provides comparison between different modalities discussed.

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## Abstract

Hepatocellular carcinoma (HCC) is an aggressive tumor that often occurs in the setting of chronic liver disease. Many patients do not initially manifest any symptoms of HCC and present late when cure with surgical resection or transplantation is no longer possible. For this reason, patients at high risk for developing HCC are subjected to frequent screening processes. The surgical management of HCC is complex and requires an inter-disciplinary approach. Hepatic resection is the treatment of choice for HCC in patients without cirrhosis and is indicated in some patients with early cirrhosis (Child-Pugh A). Liver transplantation has emerged in the past decade as the standard of care for patients with cirrhosis and HCC meeting Milan criteria and in select patients with HCC beyond Milan criteria. Loco-regional therapy with transarterial chemoembolization, transarterial embolization, radiofrequency ablation and other similar local treatments can be used as neo-adjuvant therapy to

## INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive tumor that often occurs in the setting of chronic liver disease and cirrhosis. It is the fifth most frequently diagnosed cancer worldwide and the third leading cause of cancer death<sup>[1]</sup>. Traditionally the rates of HCC in North America have been low compared to Asian and sub-Saharan African countries (15 per 100000 in Asia and Africa compared to less than 3 per 100000 in North America)<sup>[1,2]</sup>. However, the last two decades have seen a significant increase in the incidence of HCC in the United States where the risk of HCC is linked significantly to chronic viral hepatitis (hepatitis C virus and hepatitis B virus), alcohol consumption and nonalcoholic fatty liver disease<sup>[3-7]</sup>. The presence of these risk factors predisposes

**Table 1 American liver tumor study group modified tumor-node-metastasis staging classification for hepatocellular carcinoma**

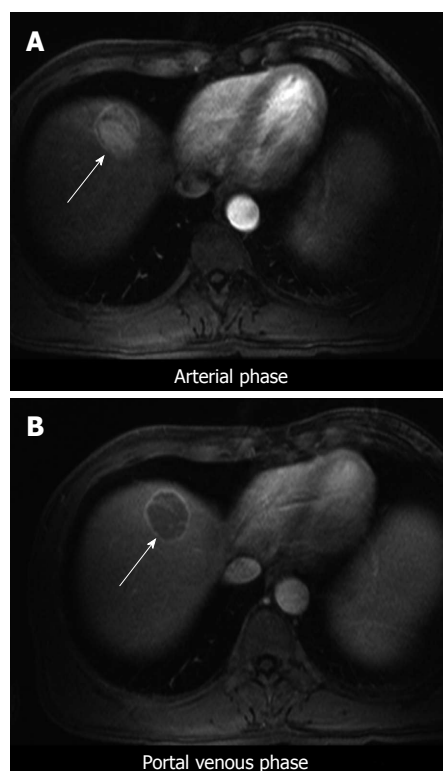
Tumor classification	Definition	Stage	Criteria
T0, N0, M0	No tumor found		
T1	1 nodule < 2.0 cm	Stage I	T1 lesion
T2	1 nodule 2-5 cm, 2 or 3 nodules each less than 3 cm	Stage II	T2 lesion
T3	1 nodule > 5 cm, 2 or 3 nodules, at least 1 > 3 cm	Stage III	T3 lesion
T4a	≥ 4 nodules, any size	Stage IVa1	T4a
T4b	T2, T3 or T4a plus gross intrahepatic, portal or hepatic vein involvement as indicated by CT, MRI or US	Stage IVa2	T4b
N1	Regional (porta hepatis) node involvement	Stage IVb	Any N1 or M1
M1	Metastatic disease including extrahepatic portal or hepatic vein involvement		

HCC: Hepatocellular carcinoma; CT: Computed tomography; MRI: Magnetic resonance imaging; US: Ultrasound; TNM: Tumor node metastasis.

patients to the development of cirrhosis and HCC by the common pathway of inducing chronic inflammation of the liver, which acts as the backdrop for genetic mutations to amass and drive cells towards malignancy<sup>[8]</sup>. The American Association for the Study of Liver Diseases (AASLD), Asian Pacific Association for the Study of the Liver and the European Association for the Study of the Liver, all have well defined guidelines for diagnosis and management of HCC which are fairly similar to each other other than some minor differences based on disease etiology and epidemiology<sup>[9-11]</sup>.

## DIAGNOSIS

Patients who develop HCC often have no symptoms other than those related to chronic liver disease. Therefore it is not unusual for HCC to be diagnosed in advanced stages (Table 1) when cure with surgical resection or transplantation is no longer possible. For this reason, patients at high risk for developing HCC are subjected to regular screening with ultrasound and tumor markers in accordance with the updated guidelines of AASLD<sup>[11]</sup>. Patients with high index of suspicion for HCC on screening then undergo additional non-invasive testing with either contrast enhanced computed tomography (CT) or gadolinium enhanced magnetic resonance imaging (Figure 1). These imaging modalities can reliably establish the diagnosis of HCC in most patients without the need for biopsy and also provide information on the size and number of lesions, relationship with vascular structures and evidence of extra-hepatic spread. Additionally, chest CTs and bone scans are routinely used to assess for metastatic disease. Traditionally Positron emission tomography scan has had a limited role in HCC staging as HCC has shown variable degrees of fluorodeoxyglucose (FDG) uptake, which lim-



**Figure 1** Magnetic resonance imaging of hepatocellular carcinoma in segment 8. Arterial enhancement (A, arrow), washout and pseudocapsule (B, arrow).

its sensitivity<sup>[12]</sup>. However recent application of PET using <sup>11</sup>C-Acetate and <sup>18</sup>F-FDG has shown it to be an effective HCC staging modality especially in patients with high alpha fetoprotein levels, primary lesions with high SUV max values and for lesions beyond Milan criteria<sup>[13,14]</sup>.

Cirrhosis of the liver underlies HCC in almost 90% of cases and the extent of underlying cirrhosis plays a vital role in determining treatment options and overall outcomes<sup>[7]</sup>. Traditionally, surgical resection has been the only option for cure but more often than not, the extent of HCC or the degree of underlying parenchymal disease precludes surgical resection. In the last two decades, liver transplantation has emerged as an effective and viable option for treatment of HCC in select patients who otherwise would not have been candidates for surgical resection<sup>[7]</sup>. Other therapies such as radiofrequency ablation (RFA), microwave ablation, transarterial embolization (TAE) and transarterial chemoembolization (TACE) can be used alone or in combination with surgical resection or transplantation to effectively treat selected patients with HCC. Tables 2 and 3 provide a brief summary of the indications, advantages and disadvantages of the commonly used treatment options for management of HCC in North America today.

## HEPATIC RESECTION

### Introduction

Hepatic resection has been the standard treatment for HCC in selected patients with limited disease and early

**Table 2** Current indications of commonly used treatment options for hepatocellular carcinoma

Current indications	
Hepatic resection	Treatment of choice in patients with resectable disease and absence of cirrhosis Indicated in selected patients with limited disease and early cirrhosis (Child-Pugh A) Limited role as a bridge to OLT
OLT	Standard therapy for patients with HCC and Cirrhosis within Milan criteria OLT may be indicated in select patients with tumors outside Milan criteria but within UCSF criteria Indicated in select patients with stage III and IV HCC downstaged to within Milan criteria with use of neo-adjuvant therapy
Non resectional ablative therapies (RFA, microwave, TACE, TAE, HIFU <i>etc.</i> )	Indicated as primary therapy only in patients with HCC who are not candidates for curative resection or OLT Increasingly used alone or in combination as bridging therapy in patients awaiting OLT or to downstage stage advanced stage disease to within Milan criteria Established role in palliative treatment of HCC (not discussed in this paper)

HCC: Hepatocellular carcinoma; OLT: Orthotopic liver transplant; UCSF: University of California San Francisco.

**Table 3** Overview of the common modalities used in the treatment of hepatocellular carcinoma

Treatment modality	Advantages	Disadvantages
Hepatic resection	Readily accessible No waiting period 5 yr survival of > 50% in carefully selected patients Peri-operative mortality < 5% Not limited by tumor size	Not indicated for patients with advanced cirrhosis High recurrence rates (> 50% at 5 yr) Risk of post operative hepatic failure Does not address risk of cancer in residual liver
OLT	Low rate of recurrence in carefully selected patients Post transplant survival rates similar to patients with OLT for all other causes	Restricted by size and number of lesions Risk of dropout while on wait list (38% drop out rate after 12 mo)
TACE/TAE	Indicated for treatment in patients not candidates for resection or OLT Effective role as bridge for transplantation Established role in downstaging HCC to make patients OLT eligible Evidence of survival benefit after OLT when used as neo-adjuvant therapy in select patients	Low curative potential when used alone with high recurrence rates Efficacy decreased for large sized tumors Does not address risk of cancer in residual liver
RFA	Relatively low morbidity Highly effective for HCC $\leq$ 3 cm	Decreased effectiveness in HCC $\geq$ 4 cm with high recurrence rates
	Effective bridge for OLT by decreasing drop out rate on wait list Established role in downstaging HCC to make patients OLT eligible Relatively low morbidity and mortality	May be limited by proximity of HCC to vascular pedicles Does not address risk of cancer in residual liver

HCC: Hepatocellular carcinoma; OLT: Orthotopic liver transplantation; TACE: Transarterial chemoembolization; TAE: Transarterial embolization; RFA: Radiofrequency ablation.

cirrhosis (Child-Pugh A)<sup>[15,16]</sup>. With advances in surgical technique and better understanding of disease pathophysiology, resection for HCC can now safely be performed in most major centers with a peri-operative mortality rate of less than 5%<sup>[15-17]</sup>. Moreover, five-year survival rates of over 50% have been reported in carefully selected patients with small, solitary tumors and well-preserved hepatic function, which supports the therapeutic role of resection in the treatment algorithm<sup>[17-19]</sup>.

### Advantages and disadvantages

In theory, hepatic resection for HCC has several advantages when compared to other therapeutic modalities such as liver transplantation and thermal ablation. It is more readily applicable, does not have an associated waiting time, and is not restricted by tumor size or proximity to hepatic veins and portal pedicles<sup>[15-20]</sup>. The effective-

ness of the surgery can be gauged early by tumor free margins on pathologic analysis and the ability to maintain an adequately functioning liver remnant. However, not every patient with localized HCC is a candidate for resection. Moreover resection does not address the remnant liver, which remains at risk for developing cancer<sup>[15,17,21]</sup>.

### Prognostic factors

Currently, surgery is preferred in patients with HCC without any underlying liver disease and in select patients with early cirrhosis (Child-Pugh A)<sup>[16,17]</sup>. The extent of underlying liver dysfunction has repeatedly been shown to be an important determinant of overall outcome with peri-operative morbidity and mortality being directly proportional to the degree of cirrhosis<sup>[18,19]</sup>. Parenchymal disease dictates the amount of resection that can be safely done without risking post-operative hepatic failure due to

a small liver remnant<sup>[18,19,21]</sup>. Cirrhosis also increases the risk of peri-operative bleeding and the need for blood transfusions, factors shown to be independently associated with increased morbidity and mortality<sup>[15,20]</sup>.

The size of HCC and total number of lesions are important determinants of outcome after hepatectomy<sup>[15,18,22]</sup>. Zhou *et al.*<sup>[16]</sup>, in their review of 1000 patients undergoing hepatectomy for HCC observed that patients with tumors greater than 5 cm had a significantly lower survival when compared to those with smaller lesions (37% *vs* 63%). Similarly, Fong *et al.*<sup>[17]</sup> reported five-year survival of 57% for patients with resected lesions less than 5 cm and only 32% for patients with tumors greater than 10 cm. However, a more recent study from the same group showed that in carefully selected patients with large tumors (> 10 cm), resection can achieve similar overall survival and recurrence-free survival as patients with smaller tumors<sup>[23]</sup>. Multi-focal or multi-nodular HCC is a poor prognostic sign and hepatectomy in these patients is associated with high recurrence rates (> 90%) and poor survival (< 30%)<sup>[18,19,24]</sup>.

Vascular invasion has repeatedly been shown to be one of the strongest negative prognosticators in patients undergoing hepatectomy for HCC<sup>[20,25,26]</sup>. Lang demonstrated 1, 3 and 5-year survival rates of 57%, 16% and 6% respectively in patients undergoing resection for HCC with vascular invasion compared to 93%, 75% and 53% in patients without vascular invasion<sup>[20]</sup>. Five-year survival after hepatectomy in patients with vascular invasion may be increased to over 20% in the absence of underlying liver fibrosis<sup>[26]</sup>.

There have been many studies looking at the impact of resection margin on recurrence and survival after HCC resection. Though there is universal consensus that an R0 resection is better than a resection with positive margins, there are no clear-cut guidelines on the minimum negative margin required<sup>[20]</sup>. A recent randomized trial compared resection outcomes for solitary HCC by randomizing 169 patients to undergo hepatic resection with either narrow (1 cm) or wide (2 cm) resection margins. Both groups were matched for tumor size. The authors reported significantly improved survival and reduced tumor recurrence in the wide margin group<sup>[27]</sup>. A more recent meta-analysis did not show a significant difference in outcomes after hepatectomy for HCC between resection margins less than 1 cm and margins equal to or greater than 1 cm<sup>[28]</sup>.

Some additional factors associated with reduced survival after hepatectomy for HCC include presence of satellite lesions or intra-hepatic metastases, poor tumor differentiation, elevated alkaline phosphatase levels and high serum alpha-fetoprotein levels<sup>[18,19,22,25]</sup>.

There have been several reports recently on laparoscopic resections for HCC. Most of these reflect highly selected patients with isolated and easily accessible disease, which makes direct comparison with open resection difficult<sup>[29,30]</sup>. A recent multicenter cohort study from France reviewed results of laparoscopic resection

for hepatocellular carcinoma in 351 patients. Eighty five percent of the patients had underlying liver disease and 11% had major hepatectomy. They reported 30-d post-operative mortality of 2%. Ninety two percent had R0 resection and reported overall 1, 3 and 5-year survivals of 90.3%, 70.1% and 65.9% respectively. These results compare favorably with the reported outcomes after open resection<sup>[29]</sup>.

### **HCC in early cirrhosis: Resection vs OLT**

The use of resection for patients with early cirrhosis (Child-Pugh A) and HCC that falls within the Milan criteria is a controversial decision at most US centers as these patients may instead be candidates for transplantation. Studies comparing the two modalities show comparable overall adjusted survival. The higher recurrence rate after resection is balanced by the risk of dropout due to disease progression in patients awaiting OLT<sup>[21,31,32]</sup>. At most centers this decision is made on a case-to-case basis after discussion in multi-disciplinary meetings and tumor boards.

### **Hepatic resection as a bridge to orthotopic liver transplantation**

Several groups have studied surgical resection as a bridge to transplantation (this will be discussed more in the section on transplantation). One concerning trend noted in many of these studies is the high number of patients (> 30%) with recurrent HCC after liver resection that is beyond the Milan criteria, making them ineligible for transplantation at most centers<sup>[33-35]</sup>. However, survival after salvage liver transplantation for patients with recurrences within Milan Criteria has shown to be comparable to survival after primary orthotopic liver transplantation (OLT) in a recent meta-analysis of 1508 patients, making it a reasonable option in carefully selected patients<sup>[36]</sup>.

## **LIVER TRANSPLANT**

### **Introduction**

Liver transplantation is now considered standard therapy for selected patients with early stage HCC and liver cirrhosis<sup>[12,21]</sup>. Initial experience with liver transplantation for HCC resulted in dismal outcomes. High recurrence rates (65%-75%) and poor survival seen in these early reports considerably diminished the interest in liver replacement for hepatic malignancy and a moratorium was placed on liver transplantation for HCC outside of clinical trials in 1989<sup>[37-39]</sup>.

### **Milan criteria for transplantation for HCC**

Interest in liver transplantation for HCC was renewed in 1996, when Mazzaferro and his group showed survival after liver transplantation in patients with cirrhosis and early-stage HCC to be comparable to results after liver transplantation in patients with benign disease<sup>[40]</sup>. This prospective cohort study included 48 cirrhotic patients who underwent transplantation for HCC with single tumors less than or equal to 5 cm or up to 3 tumors, each 3



cm or less in diameter. The actuarial 4-year survival was 75%, which was not different from expected survival of patients with non-malignant indications<sup>[40]</sup>. This study formed the basis for the Milan criteria. These results were validated by several studies and interest in transplantation as a therapeutic option for patients with early stage HCC was renewed.

### **Model for end stage liver disease allocation and exception points for HCC**

Currently in the US, livers are allocated for transplantation using the model for end stage liver disease (MELD) score, which predicts the three-month mortality of patients awaiting liver transplantation. Realizing that the MELD system would be of little benefit to patients with compensated cirrhosis and early stage HCC, UNOS in 2002 adopted the Milan criteria for allocating exception points to patients with HCC listed for liver transplantation. At the present time, patients with stage 2 HCC (Milan criteria - 1 nodule up to 5 cm or 3 nodules with the largest one 3 cm or less) can receive 22 MELD exception points which decreases the wait time for receiving a liver to between 6 mo and 12 mo at most transplant centers in North America<sup>[37,41]</sup>. Currently patients with cirrhosis and HCC beyond Milan criteria do not qualify for MELD exception points despite otherwise meeting criteria for OLT. These patients can be listed for OLT based on their original MELD score, however the likelihood of timely OLT before HCC progression is small without allocation of priority points. Transplant centers can selectively petition regional review boards for MELD exception points in HCC patients exceeding Milan Criteria or in those who have been effectively down-staged and are considered on a case to case basis<sup>[21,37]</sup>.

Results for survival and disease free interval after liver transplantation for patients have significantly improved after implementation of the Milan criteria. In a review of their 20-year experience with liver transplantation for HCC, Onaca *et al.*<sup>[42]</sup> reported an increase in five year patient survival from 28.6% in 1987-1992 and 42.3% in 1992-1997 to 76% after 1997, when Milan criteria was implemented. Similar observations were made in several other studies and as a result, the number of liver transplants performed annually in the US for HCC increased almost three fold between 2002 and 2006<sup>[21]</sup>. In most recent series, the overall five and ten year survival following transplantation for HCC is comparable to the five and ten-year survival rates for all causes<sup>[12,21,37]</sup>.

### **Extended criteria for transplantation for HCC**

In recent years there has been a push by many transplant centers for expanding the Milan criteria. It is felt that the Milan criteria is too restrictive and limits the use of transplantation to patients with very early stage HCC. Several groups have challenged these restrictions by either expanding the inclusion criteria or by using liver directed therapy to downstage patients with advanced disease to "within Milan criteria". The most notable contribution in

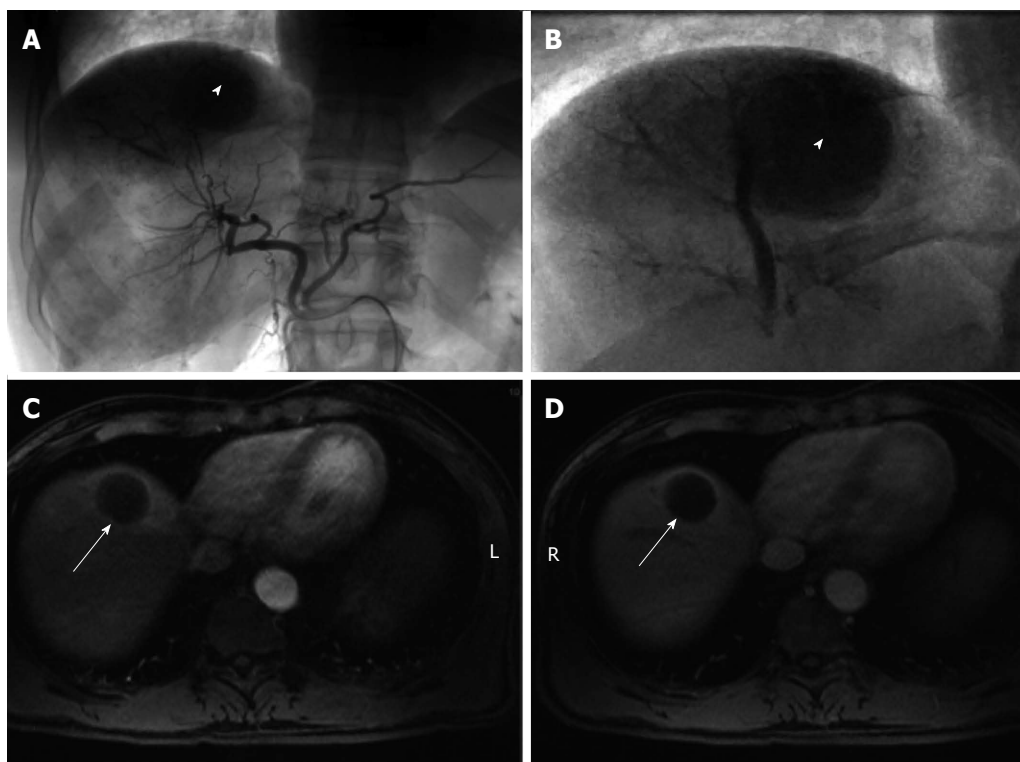
this regard came from the University of California San Francisco (UCSF) group who proposed expanding the Milan criteria to include single lesion  $\leq 6.5$  cm or up to 3 lesions, the largest  $\leq 4.5$  cm and total tumor diameter  $\leq 8$  cm without gross vascular invasion<sup>[43]</sup>. The group based their recommendations on the observation that the explant pathology often showed under-staging of HCC by preoperative cross sectional imaging and that this did not appear to impact the overall outcome. The initial paper reviewed 168 HCC patients that underwent OLT and reported a 5-year recurrence free survival of 90% for patients with tumors within Milan *vs* 94% for patients with tumors that exceeded Milan but were within the UCSF criteria<sup>[43]</sup>. A follow-up study from the same group again evaluated the expanded criteria in 467 patients and showed that patients meeting Milan criteria had similar 5-year post transplant survival to patients meeting UCSF criteria by preoperative imaging (79% *vs* 64%) and explant pathology (86% *vs* 71%)<sup>[44]</sup>. Since then several other centers have reported similar results in patients exceeding Milan criteria<sup>[45-49]</sup>.

### **Beyond UCSF?**

There is little enthusiasm for extending liver transplantation beyond the UCSF criteria as survival has shown to be significantly reduced once the size exceeds UCSF criteria<sup>[44,45]</sup>. This has led to a renewed interest in using neo-adjuvant techniques for downsizing prohibitively large HCC's in patients who may otherwise be amenable for transplantation.

### **Down-staging advanced stage HCC**

Selected patients with advanced stage HCC (stage III/IV) who are not candidates for transplantation can be down-staged with the use of neo-adjuvant loco-regional therapy to "within Milan criteria" so that they can become transplant eligible. This practice has been adopted by an increasing number of transplant centers in North America with promising results. A recent report from Washington University in St Louis demonstrated the feasibility of this approach by successfully down-staging 18 of 76 patients (23.7%) with stage III/IV disease to "within the Milan criteria" using TACE. Seventeen of these patients went on to receive OLT at a median of  $58 \pm 3.5$  mo after first TACE with an actuarial overall 5-year survival rate of 93.8%. This compared favorably to a 5-year survival rate of 66% in patients with stage II disease that were chemo-embolized and transplanted<sup>[50]</sup>. Similar results were reported by the UCSF group who utilized TACE for tumors exceeding Milan but within UCSF criteria. Forty-three of 61 patients (70.5%) were successfully down-staged, of which 35 went on to receive OLT with reported 1 and 4-year overall survival rates of 96.2% and 92.1% respectively<sup>[51]</sup>. The promising results from these two groups suggest that this strategy may help identify patients with favorable tumor biology who would carry good prognosis for long-term survival after OLT. Current recommendations call for an observation period of at least 3-6 mo after down-



**Figure 2** Treatment of hepatocellular carcinoma with transarterial chemoembolization. A, B: Angiographic images demonstrate arterial blush of hepatocellular carcinoma (HCC) (white arrowhead) with a proper hepatic arterial injection. Coned down view shows tumor blush and stasis in the segmental arteries supplying the HCC following transarterial chemoembolization (B); C, D: Follow up magnetic resonance imaging 4 wk after treatment shows no residual arterial enhancement in the treated area (white arrows) compatible with a complete response per modified response evaluation criteria in solid tumors.

staging with TACE before considering transplantation. The purpose of this observation period is to assess the biological aggressiveness of the tumor<sup>[21]</sup>.

#### **Pretreatment of patients on transplant list: Bridge to transplant**

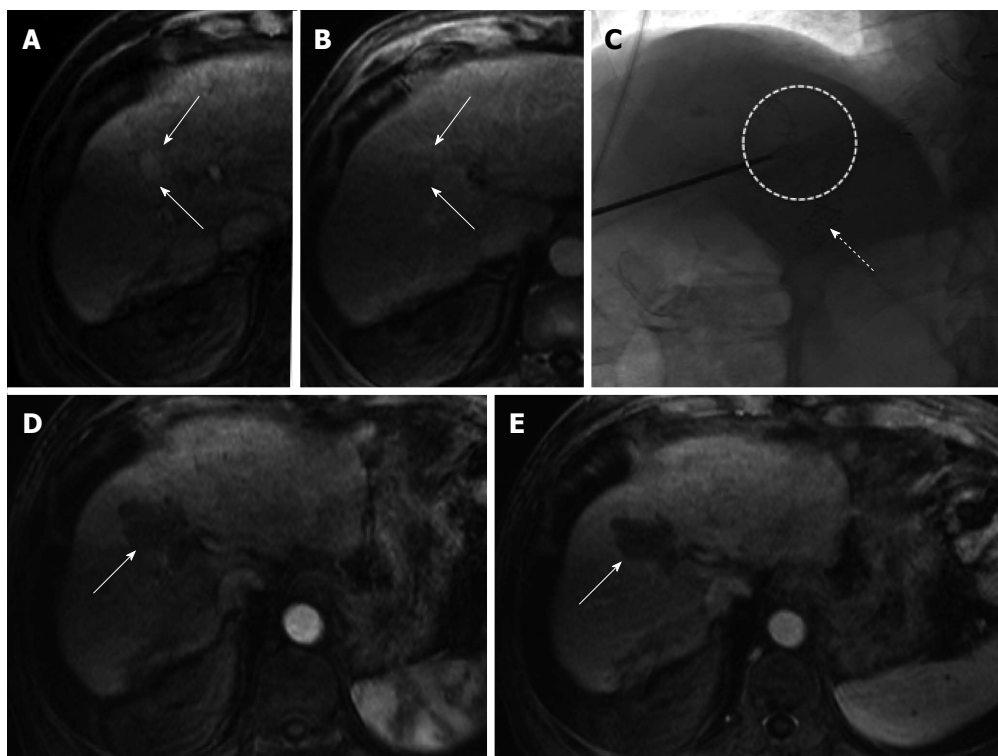
An ever-increasing demand for a relatively fixed pool of deceased donor organs has caused HCC patients to spend more and more time on the wait list. This carries a high cumulative probability of dropout due to intrahepatic or extrahepatic tumor progression. Llovet *et al.*<sup>[52]</sup> and Yao *et al.*<sup>[53]</sup> showed this probability to be between 7%-11% at 6 mo and approximately 38% at 12 mo following enrollment for OLT. Consequently, several therapeutic procedures have been proposed as bridging treatments for patients with HCC with the aims of decreasing waiting list dropout rate, reducing HCC recurrence after transplantation and improving post-transplant overall survival<sup>[54]</sup>. The most commonly used bridging modalities include TACE or TAE, ablation therapy with either RFA or percutaneous ethanol injection (PEI), and surgical resection. There are no randomized trials establishing efficacy of these treatments and clinical practices vary greatly between transplant centers.

**TACE/TAE:** TACE/TAE has a well-established role as bridging therapy for patients awaiting OLT. The most commonly used TACE procedure involves an arterial infusion of a lipiodol emulsion with a chemotherapeutic

agent (*e.g.*, doxorubicin, mitomycin or cisplatin) followed by embolization with gelfoam. Follow up cross sectional imaging is usually done 4-6 wk later to assess for completeness of ablation (Figure 2). If there is evidence of residual disease, TACE can be repeated<sup>[12,54]</sup>.

Results from most series indicate complete tumor necrosis rates of 27%-57% in patients with stage I and II disease treated with TACE<sup>[50]</sup>. There is also evidence to suggest that the use of TACE as neo-adjuvant therapy may provide survival benefit after transplantation as well. Yao *et al.*<sup>[55]</sup> demonstrated a 5-year post transplant recurrence free survival of 93.8% for patients who received preoperative loco-regional therapy *vs* 80.6% in patients who were not pre-treated. Similarly, a report by Bharat *et al.*<sup>[56]</sup> demonstrated a 5-year survival of 83.4% in pre-treated patients *vs* 51.8% in patients who did not receive any preoperative loco-regional therapy. Interestingly, both of these studies demonstrated treatment benefit only in patients with larger sized (T2-T4) tumors. Additionally, survival was highest in patients with 100% tumor necrosis in explant specimen irrespective of size<sup>[56]</sup>.

**RFA:** RFA is also being increasingly used as a bridge to transplantation in HCC patients in North America. Studies have reported complete tumor necrosis in 47%-75% of patients on explant analysis. Predictably, the rate of tumor necrosis is highest in tumors less than 3 cm<sup>[54]</sup>. Mazzaferro *et al.*<sup>[57]</sup> reported no patient drop-out due to disease progression after median waiting time of 9.5 mo



**Figure 3** Pretreatment of patients on transplant list (other modalities). A and B: Arterial enhancing hepatocellular carcinoma lesion in segment 5/8 (arrows) that shows subtle washout and possible pseudocapsule on delayed post-contrast imaging. This tumor was treated successfully using percutaneous microwave ablation; C: The tip of the microwave ablation probe positioned within the lesion (white dotted circle). Note the presence of a transjugular intrahepatic portosystemic shunt catheter (white dotted arrow) which helped direct placement of the probe on fluoroscopic images; D, E: Follow up magnetic resonance imaging 4 wk after ablation shows large ablation cavity covering the region of the previously seen tumor (arrows). There is no residual arterial enhancement suggesting complete tumor necrosis.

in 50 patients undergoing pre-transplant RFA. The 1 and 3-year post transplant survival was reported at 95% and 83% respectively.

**Liver resection:** The role of liver resection as a bridge to transplantation is controversial. Approximately 70% of patients develop recurrent disease after resection and about one-third of them recur beyond Milan criteria making them transplant ineligible at most centers<sup>[33-35]</sup>. However, survival after salvage liver transplantation for patients with recurrences within Milan Criteria was shown in a recent meta-analysis to be comparable to survival after primary OLT<sup>[56]</sup>. Currently in the United States, patients on OLT waiting list who have already undergone liver resection for HCC are not awarded MELD score exception points, which makes it a less attractive option.

**Other modalities:** PEI is one of the oldest techniques for local treatment of HCC and it is rarely used as a bridging treatment for transplantation<sup>[54]</sup>. Microwave ablation, high-intensity focused ultrasound (HIFU) ablation, percutaneous laser ablation, conformal radiotherapy and transarterial radioembolization, are some of the new and upcoming techniques that may play a role as a bridge to transplantation in the future either alone or in combination therapy with other established modalities (Figure 3). A recent pilot study showed promising results with use of HIFU ablation as bridging therapy for HCC

patients on transplant wait list who were not candidates for TACE or radiofrequency ablation. Patients in the HIFU group had comparable percentages of tumor necrosis on explant specimen to TACE patients and this technique was found to be safe even in patients with advanced cirrhosis (Child-Pugh C). It still remains to be seen whether these promising initial results will be reproduced in a RCT<sup>[58]</sup>.

### Non resectional ablative therapies

Ablative therapies have emerged in the past decade as effective treatment options for select patients with HCC. RFA and TACE/TAE are the more commonly employed ablative techniques and work by causing tumor necrosis. These techniques have shown to be reasonably effective for small tumors but also have significant limitations<sup>[15,57]</sup>. Consequently their role for primary treatment of HCC is limited at the present time for patients with advanced disease that is not amenable for resection or transplantation or in patients who are at a prohibitively high risk for major surgery. Additionally, RFA and TACE/TAE are now increasingly being used as a bridge to transplantation in an attempt to decrease dropout rate for patients on transplant waiting list. Recent reports have also supported the use of loco-regional ablative techniques to downstage patients with advanced HCC to “within Milan criteria” where they can be listed for OLT<sup>[21,50,51,56,59]</sup>.

Microwave ablation, high intensity focused ultrasound



and irreversible electroporation are some of the newer ablative techniques that will likely find a place in the treatment algorithm of HCC alongside RFA and TACE.

We will only discuss RFA under this section as others have been discussed under the section of bridging for transplantation.

**RFA:** RFA has emerged as an effective treatment option for select patients with HCC limited to the liver and who do not meet criteria for resectability. RFA has also been increasingly used along with TACE/TAE as “bridging” therapy in patients awaiting liver transplantation or to downsize patients with stage III/IV HCC to Milan criteria for subsequent liver transplantation as discussed earlier. It is performed percutaneously in the majority of cases and effectiveness varies greatly with tumor size and location<sup>[21]</sup>.

RFA involves application of thermal energy to the lesion using high frequency alternating current. As the temperature of the tumor tissue rises above 60 degrees Celsius, cells begin to die, resulting in an area of coagulative necrosis around the RF electrode. It can be used alone or in combination with TAE/TACE for management of HCC.

The HCC treatment algorithm established by the AASLD recommends ablative treatment for HCC nodules with a maximal diameter of 3 cm in patients with 3 or fewer tumors and in whom resection is otherwise contraindicated<sup>[60]</sup>. Chen *et al*<sup>[61]</sup> reported their results from a randomized control trial comparing survival between surgical resection and ablative therapy in 180 patients with solitary HCC up to 5 cm in size. They demonstrated comparable 1 and 4 year survival rates of 95.8%, 67.9% and 93.3%, 64.0% after ablative therapy and surgery respectively. The corresponding 1 and 4-year disease-free survival rates were 85.9%, 46.4% and 86.6%, 51.6% respectively. Combination therapy with TACE and RFA been shown to be safe and effective for solitary HCC's greater than 5 cm with approximate recurrence free survival times of 17 mo<sup>[59,62]</sup>.

Choi *et al*<sup>[63]</sup> reported a 5 year local recurrence rate and corresponding survival rate of 11.9% and 51.6% respectively for 101 patients with recurrent HCC after hepatectomy, who then underwent percutaneous ultrasound guided RFA. In a recent prospective randomized trial, Peng *et al*<sup>[64]</sup> demonstrated that combination therapy with TACE and RFA was more effective than RFA alone for treatment of recurrent HCC. This difference was significant for recurrent tumors greater than 3 cm in size. It is important to realize that although TACE and RFA may prolong survival, at this time they are not considered curative treatment options for HCC. Additionally like hepatic resection, ablative techniques do not address the risk of HCC in the remnant cirrhotic liver.

## CONCLUSION

The surgical management of HCC is complex and re-

quires an inter-disciplinary approach. Hepatic resection is the treatment of choice for HCC in patients without cirrhosis and is indicated in some patients with early cirrhosis (Child-Pugh A). Effectiveness of surgery is dependent on ability to achieve negative margins while maintaining an adequately functioning liver remnant. Large HCC, multifocal disease, underlying cirrhosis and vascular invasion by the tumor are some of the major factors negatively impacting outcome after surgical resection. Liver transplantation is the established standard of care for patients with cirrhosis and HCC meeting Milan criteria and in select patients with HCC beyond Milan but within UCSF criteria. Neo-adjuvant loco-regional therapy (TACE/TAE, RFA *etc.*) followed by a period of observation must be considered for patients beyond Milan criteria in an attempt to downstage them to meet Milan criteria. Loco-regional therapies (TACE/TAE and RFA) can also be used as a bridge to transplantation with favorable oncologic outcomes and reduced dropout rates in patients awaiting OLT. The role of hepatic resection as bridge for transplantation is controversial.

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